Neural stem cells genetically-modified to express neprilysin reduce pathology in Alzheimer transgenic models.

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Public Summary:
We had previously shown that transplants of mouse neural stem cells to the brains of a mouse model of Alzheimer disease corrected their behavioral and learning deficits, and implicated induction of new synapses by BDNF (brain-derived neurotrophic factor) produced by the stem cells as a causal factor. However, in that publication, we saw no change in the density of amyloid deposits in the mouse brain; amyloid plaques are a defining feature in human AD. In the current study, we engineered the stem cells so they would secrete neprilysin, a protease that degrades peptide neurotransmitters in the brain. The mice transplanted with the neprilysin-neural stem cells not only showed recovery of behavioral deficits, but the stem cells also cleared the amyloid plaque. This result suggests that stem cell derivatives may be useful for treatment of AD.

Scientific Abstract:
INTRODUCTION: Short-term neural stem cell (NSC) transplantation improves cognition in Alzheimer's disease (AD) transgenic mice by enhancing endogenous synaptic connectivity. However, this approach has no effect on the underlying beta-amyloid (Abeta) and neurofibrillary tangle pathology. Long term efficacy of cell based approaches may therefore require combinatorial approaches. METHODS: To begin to examine this question we genetically-modified NSCs to stably express and secrete the Abeta-degrading enzyme, neprilysin (sNEP). Next, we studied the effects of sNEP expression in vitro by quantifying Abeta-degrading activity, NSC multipotency markers, and Abeta-induced toxicity. To determine whether sNEP-expressing NSCs can also modulate AD-pathogenesis in vivo, control-modified and sNEP-NSCs were transplanted unilaterally into the hippocampus of two independent and well characterized transgenic models of AD: 3xTg-AD and Thy1-APP mice. After three months, stem cell engraftment, neprilysin expression, and AD pathology were examined. RESULTS: Our findings reveal that stem cell-mediated delivery of NEP provides marked and significant reductions in Abeta pathology and increases synaptic density in both 3xTg-AD and Thy1-APP transgenic mice. Remarkably, Abeta plaque loads are reduced not only in the hippocampus and subiculum adjacent to engrafted NSCs, but also within the amygdala and medial septum, areas that receive afferent projections from the engrafted region. CONCLUSIONS: Taken together, our data suggest that genetically-modified NSCs could provide a powerful combinatorial approach to not only enhance synaptic plasticity but to also target and modify underlying Alzheimer's disease pathology.